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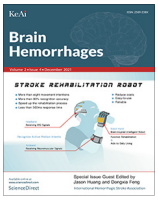

Review article

The relationship between COVID-19 infection and intracranial hemorrhage: A systematic review

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ABSTRACT

Introduction: In addition to the deleterious effects Covid-19 has on the pulmonary and cardiovascular systems, COVID-19 can also result in damage to the nervous system. This review aims to explore current literature on the association between COVID-19 and intracranial hemorrhage (ICH).
Methods: We conducted a systematic review of PubMed for literature published on COVID-19 and ICH. Ninety-four of 295 screened papers met inclusion criteria.
Results: The literature addressed incidence and mortality of ICH associated with Covid-19. It also revealed cases of COVID-19 patients with subarachnoid hemorrhage, intraparenchymal hemorrhage, subdural hematomas, and hemorrhage secondary to cerebral venous thrombosis and ischemic stroke. ICH during COVID-19 infections was associated with increased morbidity and mortality. Risk factors for ICH appeared to be therapeutic anticoagulation, ECMO, and mechanical ventilation. Outcomes varied widely, depending on the severity of COVID-19 infection and neurologic injury.
Conclusion: Although treatment for severe Covid-19 infections is often aimed at addressing acute respiratory distress syndrome, vasculopathy, and coagulopathy, neurologic injury can also occur. Evidence-based treatments that improve COVID-19 mortality may also increase risk for developing ICH. Providers should be aware of potential neurologic sequelae of COVID-19, diagnostic methods to rule out other causes of ICH, and treatment regimens.

1. Introduction

The 2019 novel coronavirus (Covid-19) pandemic has claimed nearly 5 million lives since it began in November of 2019.[1] Covid-19 infections primarily affect the respiratory system, leading to viral pneumonia via the binding of the SARS-CoV-2 spike protein to the endothelial angiotensin converting enzyme-2 (ACE-2) receptor.[101] However, severe cases of Covid-19 can lead to pathology across multiple organ systems through multiple mechanisms. One mechanism by which multiple organ systems become damaged is related to direct viral invasion, as the ACE-2 receptor is highly expressed in multiple organs, and viral replication itself can cause cell death.[16,100] A second mechanism is related to the systemic inflammatory response seen in severe cases of Covid-19 caused by cytokine dysregulation, leading to septic shock. Increased vascular permeability and extravasation of both neutrophils and lymphocytes, in combination with viral binding to endothelial cells, can also lead to vasculopathy and vasculitis.[11,100] A final mechanism by which Covid-19 can cause damage to multiple organ systems is through Covid-19 associated coagulopathy (CAC). CAC is characterized by initial elevations in d-dimer and fibrinogen, and it leads to both vascular thrombosis and parenchymal hemorrhage.[6,76]

The central nervous system (CNS) is one potential target of the Covid-19 virus, and devastating neurologic consequences of infections were reported early in the pandemic.[65] One specific pathology that can lead to these devesting neurologic consequences is intracranial hemorrhage. There has been a higher rate of intracranial hemorrhage associated with Covid-19 than other respiratory viruses, such as the influenza virus (OR 2.85, 1.35–6.02).[20] Further, when patients do suffer intracranial hemorrhage during a Covid-19 infection, they have been shown to be more likely to have a longer length of stay, to require ICU level care, to require mechanical ventilation, and to require vasopressor support.[31] Covid-19 patients that suffer a stroke or intracranial hemorrhage have also been shown to have higher mortality, especially if the patient is on mechanical ventilation.[8,68,79]

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Our knowledge and understanding of the pathophysiology of Covid-19 and its treatments is rapidly evolving. However, data on the negative effects that Covid-19 can have outside the respiratory system remains limited, particularly on the devastating consequences it can have on the CNS. Thus, we sought to review the available literature on Covid-19 and its association with intracranial hemorrhage.

2. Methods

The PubMed database was queried using the following search terms: ((“subarachnoid hemorrhage”) OR (“Intracranial Hemorrhage”) OR (“Intraparenchymal hemorrhage”) OR (“subdural hematoma”) OR (“epidural hematoma”) OR (“venous sinus thrombosis”) OR (“Sinus thrombosis”)) AND ((“severe acute respiratory syndrome”) OR (SARS) OR (SARS-COV) OR (“SARS COV”) OR (“novel coronavirus”) OR (nCoV) OR (“2019-nCoV”) OR (COVID) OR (SARS-CoV-2) OR (COVID-19)). All literature published prior to August of 2021 was then screened (N = 287). Articles were included if they addressed intracranial hemorrhage such as subarachnoid hemorrhage (SAH), intraparenchymal hemorrhage (IPH), subdural hemorrhage (SDH), or hemorrhage related to strokes and venous thrombosis. Articles were excluded if they were not available in English. Eight articles from additional sources were also included to bring the total number of screened articles (either abstract or full text) to 295. All articles were screened by one author (SD), and ninety-four papers were found to meet the inclusion criteria. They were separated into seven sections based on their reported data.

3. Results

Incidence and mortality of intracranial hemorrhage associated with Covid-19

Thirty-three articles were identified in the literature search that reported descriptive statistics on the incidence, distribution, and mortality rates of intracranial hemorrhage in various subgroups of patients with Covid-19 (Table 1).

Fifteen studies reported on these statistics in all hospitalized Covid-19 patients over a defined period of time. The rate of intracranial hemorrhage in this subgroup was reported to be between 0.1% and 3.3% (for patients > 80 years old, the rate was reported at 6.8%).[73] Nine of the studies included information on the distribution of types of intracranial hemorrhage in this population, which included SAH, IPH, intraventricular hemorrhage (IVH), hemorrhagic conversion of ischemic stroke, SDH, and multicompartment hemorrhage (MCH). In studies with more than one death, the mortality rate for hospitalized Covid-19 with intracranial hemorrhage was reported to be between 50% and 84.6%.

Five studies reported the distribution of types of intracranial hemorrhages in cohorts of patients with Covid-19. SAH and IPH represented the majority of cases in these studies, although SDH and MCH was also reported. Mortality in these cohorts was reported to be between 42.9% and 58%.

There were eight studies that analyzed these statistics in hospitalized Covid-19 patients that had some form of brain imaging. The reported incidence of intracranial hemorrhage in this subgroup was between 2.9% and 11.8%, and was associated with older age, mechanical ventilation, and therapeutic anticoagulation.[68] The mortality of hospitalized Covid-19 patients with intracranial hemorrhage in this subgroup was 29% to 42%.

Four studies included only patients on extracorporeal membrane oxygenation (ECMO) for Covid-19. They reported the rate of intracranial hemorrhage in these patients to be 16% to 42%. Of note, the rate of intracranial hemorrhage in this subgroup of patients is much higher than the rate of cerebral hemorrhage associated with veno-venous ECMO in adults for respiratory failure (3.6%).[66] The reported mortality rate of patients on ECMO for Covid-19 with an intracranial hemorrhage was 75%–82%.

Subarachnoid hemorrhage

There were nineteen studies within the literature search that specifically discussed SAH in patients with Covid-19. One was a large study was done to evaluate the risk of developing SAH during Covid-19 infections by analyzing the de-identified Covid-19 dataset from Cerner.[77] The authors interesting did not find an increased risk of SAH in Covid-19 positive patients compared to Covid-19 negative patients (0.1% vs. 0.2%). However, there was a significantly increased risk of morbidity and in-hospital mortality in Covid-19 positive patients with SAH compared to those without Covid-19 (31.4% vs. 12.2%).

The remaining 18 studies report data on a total of 33 patients, who suffered SAH during Covid-19 infection (Table 2). There were 9 patients who had an aneurysmal SAH, of which at least 4 were symptomatic from Covid-19. One of the 6 with reported outcomes died. The most common location for the aneurysm was the posterior communicating artery (N = 3). Fourteen patients were reported to have non-aneurysmal spontaneous SAH, of which ten were symptomatic from Covid-19. Five of the 10 patients with symptomatic Covid-19 died. All three with asymptomatic Covid-19 died, and two of the deaths were from subsequent respiratory failure.

One case series is not included in Table 2, because data for the patients is largely aggregated.[32] This case series reports on ten patients with aneurysmal SAH and active or recent Covid-19 diagnosis that presented to one of five cerebrovascular centers over 10 months. Three of the ten patients had severe Covid-19, and four were asymptomatic. Five patients had saccular aneurysms, four had dissecting pseudoaneurysms, and one had a blister aneurysm. Two patients underwent surgical clipping, four underwent aneurysm coiling, three underwent flow diversion, and one patient died prior to treatment. Two of the ten patients died (both had high grade SAH), and seven were discharged with mRS 0–2.

Intraparenchymal hemorrhage

Presentation with Respiratory symptoms

There were nine studies identified that reported information on seventeen patients, who were in the hospital with respiratory symptoms related to Covid-19, and subsequently developed IPH (Table 3). Ten of the seventeen patients were male (58%), and the patients were between the ages of 38 and 74. Thirteen patients were intubated, and four were on ECMO. All seventeen of the patients were on some form of anticoagulation, and thirteen of the seventeen were on therapeutic anticoagulation (76%). The most common type of IPH was unilateral lobar (N = 9), followed by unilateral lobar with intraventricular extension (IVE) (N = 2), bilateral lobar (N = 2), and focal IPH (N = 2, corpus callosum and posterior fossa). One patient had a bilateral lobar IPH with IVE. Mortality was reported in 9 of the 15 patients for whom outcome was reported (mortality rate 60%). Of the six with reported outcome that did not die, two discharged to rehabilitation (one with severe deficits), three had a reported modified Rankin Scale (mRS) of 5, one had a reported mRS of 4.

Presentation with Neurologic symptoms

Five studies were identified that reported information on seven patients, who presented to the hospital with neurologic symptoms related to IPH and were found to have asymptomatic Covid-19 (Table 3). Three patients presented to the hospital with primary

Table 1
Incidence, Distribution, and Mortality of Intracranial Hemorrhage in Covid-19 Patients.

Study	Population	Incidence	Distribution of Hemorrhage	Mortality
		All Hospitalized Patients with Covd-19		
Rothstein, et al.[82]	N = 844	0.95%	63% IPH 37% SAH	75% (6 of 8)
Siegler, et al. [90]	N = 14,483	0.29%	47% IPH 33% Hemorrhagic Conversion 19% IVH 17% SAH 5% SDH	58.3% (Mortality from Intracranial hemorrhage)
Shekhar, et al.[88]	N = 90	3.3%	67% IPH with IVE and SAH 33% SAH	67% (2 of 3)
Kvernland, et al.[57]	N = 4071	0.8%	44% Hemorrhagic Conversion 17% Punctate Hemorrhages 15% IPH with IVE and SAH 9% IPH 9% SAH 6% IPH with IVE	84.6%
Sabayan, et al.[85]	Physician-reported cases over 1 month in Iran	N = 1	100% SAH	100% (1 of 1)
Le, et al.[60]	N = 35,177	0.5%	40% SAH 40% Intracerebral hemorrhage 20% intracranial hemorrhage	–
Katz, et al. [49]	N = 10,596	0.26%	50% Intracranial hemorrhage 39% Combined intracranial hemorrhagic and ischemic stroke 21% Hemorrhagic conversion	
Shahjouei, et al.[86]	N = 17,799	0.15%	93% Intracerebral Hemorrhage 7% SAH	
Dhamoon, et al.[31]	N = 5,469	0.3%	80% Intracerebral Hemorrhage 20% SAH	
Altschul, et al.[8]	N = 5,227	0.7%	49% SDH 26% IPH 20% MCH 6% SAH	
Requena, et al.[81]	N = 2,050	0.2%	–	50% (2 of 4)
Mao, et al.[65]	N = 214	0.47%	–	100% (1 of 1)
Nabors, et al.[73]	N = 73 (>80 years old)	6.8%	–	–
Cates, et al.[20]	N = 3,948	0.7%	–	–
Chuang, et al.[24]	N = 2,414	0.1%	–	–
		Symptomatic Intracranial Hemorrhage in Hospitalized Patients with Covid-19		
Nawabi, et al.[74]	N = 18	–	50% SAH 33% IPH 11% IVH 5% SDH/SAH	44.4% (8 of 18)
		Covid-19 Positive Patients with Hemorrhage		
Trifan, et al. et al.[95]	N = 19	–	85% ICH 15% SAH	53% (10 of 19)
Shahjouei, et al.[87]	N = 91	–	67% IPH 25% SAH 8% MCH	50% (17 remained in the hospital)
Abbas, et al.[2]	N = 19	–	63% IPH 31% SAH (21% aneurysmal) 5% SDH	58% (11 of 19)
Ravindra, et al.[79]	N = 559 ICH N = 212 SAH	–	–	ICH: 46% SAH: 42.9%
		Covid-19 Patients with Brain Imaging		
Kelsch, et al.[52]	N = 648	3.2%	38% Hemorrhagic conversion 29% IPH 29% SDH 5% SAH	42% (6 of 14 with hemorrhagic conversion or IPH)
Radmanesh, et al.[78]	N = 242	2.9%	57% Chronic Hemorrhage 29% IPH 14% Hemorrhagic Conversion	29%
Klironomos, et al.[56]	N = 213	9% in those with CT 28% in those with MRI	CT: 69% IPH 50% SDH 31% SAH 13% EDH MRI: 82% SAH 18% IPH	–

(*continued on next page*)

Table 1 (*continued*)

Study	Population	Incidence	Distribution of Hemorrhage	Mortality
Lang, et al.[58]	N = 93	11.8%	64% ICH 36% ICH and Infarct	–
Mahammedi, et al.[63]	N = 135	10%	50% Microhemorrhage 29% SAH 21% IPH	–
Greenway, et al.[41]	N = 180	3.3%	67% Intracranial Hemorrhage 33% Hemorrhagic Conversion	
Buttner, et al.[17]	N = 34	9%	–	–
Melmed, et al.[68]	N = 416	7.9%	–	–
		Covid-19 Patients with Neurologic Manifestations		
Varatharaj, et al.[99]	N = 153	5.9%	–	–
		Covid-19 Patients on ECMO		
Usman, et al.[97]	N = 10	40%	25% IPH 25% IPH with IVE 25% IPH with SAH 25% SAH	75% (3 of 4)
Doyle, et al.[33]	N = 51	16%	88% SAH 12% SDH	–
Bermea, et al.[14]	N = 33	33%	–	82%
Masur, et al.[66]	N = 12	42%	–	–

Abbreviations: N = sample size, IPH = Intraparenchymal Hemorrhage, SAH = Subarachnoid hemorrhage, IVE = Intraventricular Extension, IVH = Intraventricular Hemorrhage, SDH = Subdural hematoma, ECMO = Extracorporeal Membrane Oxygenation, ICH = Intracerebral Hemorrhage.

Table 2
Subarachnoid Hemorrhage.

		Aneurysmal SAH, Asymptomatic Covid-19		
Study	Age, Sex	Aneurysm	Treatment	Outcome
Alam, et al.[7]	38, F	P-Comm	Not Reported	Discharged Home
Rustemi, et al.[83]	68, F	P-Comm (HH1, Fisher II)	Standard of Care	Discharged without deficit
Muhammad, et al.[72]	60, F	Pericallosal (Fisher IV)	Surgical Clipping	Rehabilitation
Estevez-Ordonez, et al.[35]	56, F	MCA bifurcation (Fisher I)	Surgical Clipping	mRS 1
		Aneurysmal SAH, Symptomatic Covid-19		
Study	Age, Sex	Aneurysm	Treatment	Outcome
Shojaei, et al.[89]	55, F	A-Comm	EVD, delayed aneurysm treatment	Death
Cezar-Junior, et al.[21]	36, F	Saccular ICA (Fisher IV)	Embolization	mRS 4
		Aneurysmal SAH, Unknown Covid-19 Symptoms		
Study	Age, Sex	Aneurysm	Treatment	Outcome
Sweid, et al. [92]	Unknown	PICA (HH3)	Flow Diversion	Unknown
	Unknown	P-Comm (HH4)	Surgical Clipping	Unknown
	Unknown	Anterior choroidal artery aneurysm	Flow Diversion	Unknown
		Non-Aneurysmal SAH, Asymptomatic Covid-19		
Study	Age, Sex	Diagnosis	Treatment	Outcome
Alam, et al.[7]	63, M	–	–	Death due to Respiratory Failure
Craen, et al.[25]	66, F	Acute Hemorrhagic Necrotizing Encephalitis	Aggressive cardiopulmonary support	Brain Death
Avci, et al.[9]	50, M	Parasagittal SAH with IVE	Intubated	Death due to Respiratory Failure
		Non-Aneurysmal SAH, Symptomatic Covid-19		
Study	Age, Sex	SAH Description	Covid-19 Course	Outcome
Agarwal, et al.[3]	41, F	SAH associated with cytotoxic lesion in corpus callosum	Respiratory Support	Death due to cardiac complications
Haider, et al.[42]	56, M	Bilateral SAH with IVE (unruptured pericallosal aneurysm on cerebral angiography)	Had just been decannulated from ECMO and was on therapeutic anticoagulation for Pulmonary Embolus	Recovered without neurologic deficits
Zulfiqar, et al.[103]	65, F	Frontal SAH	Developed immune thrombocytopenic purpura	Recovered
Harrogate, et al.[43]	74, M	Multifocal SAH	Intubated	Rehabilitation
	53, M	Multifocal SAH	Intubated	Rehabilitation
Dakay, et al.[28]	30′s, F	Bilateral SAH from RCVS	Dry cough	Discharged Home
Basirjafari, et al.[10]	9, M	Diffuse SAH with cerebral edema and no vessel abnormalities	Intubated	Brain Death
Fayed, et al.[36]	54, F	Diffuse SAH with IVE and sulcal effacement	Intubated	Brain Death
Mousa-Ibrahim, et al.[70]	79, M	Bilateral cortical SAH and diffuse ischemic injury	Intubated	Brain Death
Cezar-Junior, et al.[21]	53, M	Fisher III SAH	Did not require intubation	mRS 2
	61, F	Fisher IV SAH	Intubated for Neurologic decline	Death

Abbreviations: M = male, F = female, SAH = Subarachnoid hemorrhage, mRS = modified Rankin Score, P-Comm = Posterior communicating artery, A-comm = Anterior communicating artery, PICA = Posterior inferior cerebellar artery, MCA = Middle cerebral artery, ICA = Internal carotid artery, HH = Hunt Hess, RCVS = reversible cerebral vasoconstriction syndrome

Table 3
Intraparenchymal Hemorrhage.

Patients Presenting with Respiratory Symptoms					
Study	Age, Sex	Covid-19 Treatment	Anticoagulation	IPH	Outcome
Ghani, et al.[38]	59, F	Intubated	Therapeutic Enoxaparin	Frontal IPH with IVE	Brain Death
Charra, et al.[23]	61, M	Intubated	Therapeutic Heparin	Corpus Callosum	Not reported
Chalil, et al.[22]	41, F	Intubated	Heparin Infusion	Bilateral Parietal and Occipital IPH with IVE	Rehabilitation with "severe" deficits
Khattar, et al.[53]	43, M	Intubated	Heparin Infusion	Multiloculated IPH in Right Hemisphere	Brain Death
Carroll, et al.[19]	62, M	Intubated	Heparin Infusion	Multifocal IPH with IVE	Brain Death
	74, M	Intubated	Heparin Infusion	Multi-lobar IPH	Brain Death
Fayed, et al.[36]	57, F	Intubated	Heparin Infusion	Right Frontal IPH	Rehabilitation
Mousa-Ibrahim, et al.[70]	54, F	Intubated	Prophylactic LMWH	Posterior fossa	Brain Death
	71, F	Intubated	Prophylactic LMWH	Frontal Lobe	Brain Death
Benger, et al.[12]	41, M	Intubated	Prophylactic LMWH	Frontal Lobe	mRS 4
	50, M	Intubated	Prophylactic LMWH	Frontal Lobe	mRS 5
	64, F	Intubated	Heparin Infusion	Basal ganglia	mRS 5
	52, M	Intubated	Heparin Infusion	Bilateral Multi-lobar IPH	mRS 5
Zahid, et al.[102]	38, M	ECMO	Therapeutic Heparin	Small sub-insular IPH	IPH resolved
Heman-Ackah, et al.[44]	58, F	ECMO	Therapeutic Heparin	Frontal (90 mL)	Brain Death
	46, M	ECMO	Therapeutic Heparin	Frontal (118 mL)	Brain Death
Motoie, et al.[69]	50, M	ECMO	Heparin Infusion	Multifocal, Bilateral IPH's	Brain Death
Patients Presenting with Neurologic Symptoms					
Study	Age, Sex	Relevant History	Presenting Symptoms	IPH	Outcome
Benger, et al.[12]	54, F	Warfarin for a history of DVT/PE	Dysarthria, Hemiparesis	Frontal Lobe	mRS 5
Flores, et al.[37]	40, M	Hypertension, Obesity	Confusion and Somnolence	Pons and Midbrain with IVE	Brain Death
Thu, et al.[94]	72, M	None	Seizures, Loss of Smell	Right Olfactory Gyrus	Symptoms Resolved
Degeneffe, et al.[30]	72, M	None	- Repetitive falls - Necrotic Lesion in Corpus callosum (Stereotactic Biopsy, WHO grade IV)	Post-operative IPH	Brain Death
	63, M	On ASA	- Seizure. - Right lobar cystic-necrotic lesion (Stereotactic Biopsy, WHO grade III)	Post-operative IPH	Brain Death
	78, M	Prostate Adenocarcinoma	- Headaches, Confusion, Hemihypoesthesia - Focal Meningeal Enhancement (Meningeal Biopsy)	Post-operative Occipital IPH	Brain Death
Engert, et al.[34]	Day 1 of Life	- Preterm labor at 33 weeks - Negative PCR test for Covid-19 - Maternal serum test positive for IgG of S1-protein and N-protein	Preterm labor	Bilateral Cortical Hemorrhages	Discharged with no Neurologic Deficits

Abbreviations: M = male, F = female, IPH = intraparenchymal hemorrhage, IVE = intraventricular extension, mRS = modified Rankin Score, WHO = World Health Organization, DVT/PE = deep vein thrombosis/pulmonary embolism, LMWH = low molecular weight heparin

neurologic symptoms, and each was found to have an IPH of variable severity. The patient with the brain stem hemorrhage died, the patient with the frontal lobe IPH discharged with mRS 5, and the patient with the olfactory gyrus hemorrhage recovered. A case series reported three patients, who had positive pre-operative Covid-19 PCR tests, and subsequently died from IPH after cranial biopsies0.[30] Of note, Anti-SARS-Cov tests were negative on cerebral samples from all three patients. The authors reported that 28 cranial biopsies had been done on Covid-19 negative patients during the same time, and none of those patients had any complication. The final study describes a newborn child born at 33 weeks due to pre-term labor, who was found to have bilateral cortical hemorrhages.[34] The patient had a negative PCR test for Covid-19, but maternal serum was positive for IgG of the SARS-CoV-2 S1-protein and N-protein.

Subdural hematoma

Two patients were identified in two separate articles that suffered a SDH during a Covid-19 infection. The first was in a case report of a 50-year-old Covid-19 positive male admitted for treatment of newly diagnosed acute promyelocytic leukemia, who developed an acute SDH with 12 mm of midline shift. He underwent decompressive craniotomy and passed away after surgery due to disseminated intravascular coagulopathy (DIC). The authors concluded that the SDH would have been unlikely without a simultaneous diagnosis of Covid-19.[39] The second case was identified in a single institution case series of Covid-19 patients with a devastating neurologic outcome. This patient was a 68-year-old female, who was incidentally found to be Covid-19 positive, and presented with a spontaneous SDH, requiring neurosurgical decompression. She suffered a post-operative IPH likely due to a cortical vein thrombosis, but she was eventually discharged to rehabilitation.[70]

Multicompartment Hemorrhages

Five studies reported on eight Covid-19 patients, who developed simultaneous MCH (Table 4). Seven of the 8 patients presented with respiratory symptoms. Within that group, five were male, and they were all between the ages of 59 and 76. Five of

Table 4
Multicompartment Hemorrhages.

Study	Age, Sex	Primary Symptoms	Anticoagulation	Bleed	Outcome
Gogia, et al.[40]	75, M	Respiratory	Aspirin, Clopidogrel, therapeutic enoxaparin	- SDH - Temporal IPH (100 mL) - SAH	Brain Death
Al-Olama, et al.[5]	36, M	Neurologic (Covid-19 RNA in CSF)	–	- IPH - SAH - Small SDH	Surgical Decompression
Ghani, et al.[38]	59, M	Respiratory	–	- IPH (posterior fossa) - SAH	Brain Death
	61, F	Respiratory	–	- SDH - Diffuse SAH	Brain Death
Soldatelli, et al.[91]	67, M	Respiratory	Prophylactic Enoxaparin	- IPH with IVE - Corpus Callosum Microbleeds - SAH	Rehabilitation
	71, F	Respiratory	–	- SAH - Interhemispheric SDH	Rehabilitation (mRS 4)
Mousa-Ibrahim, et al.[70]	76, M	Respiratory	Therapeutic LMWH	- IPH with IVE - SAH - Cerebellar IPH - (1.3 cm MLS)	Brain Death
	63, M	Respiratory	Therapeutic LMWH	- Bilateral IPH with IVE - SAH - Parietal infarct with hemorrhagic conversion	Brain Death

Abbreviations: M = male, F = female, RNA = ribonucleic acid, CSF = cerebral spinal fluid, SDH = subdural hematoma, IPH = intraparenchymal hemorrhage, SAH = subarachnoid hemorrhage, IVE = intraventricular extension, mRS = modified Rankin Score

Table 5
Hemorrhages associated with Cerebral Venous Thrombosis.

			Patients with Active Covid-19 Infections			
Study	Age, Sex	Presenting Symptoms	Anticoagulation at the time of the CVT	CVT	Hemorrhage	Outcome
Keaney, et al.[51]	51, M	Respiratory (Intubated)	Dual antiplatelet therapy and anticoagulation	Superior Sagittal Sinus	Hemorrhagic Infarction	Brain Death
	72, F	Respiratory (Intubated)	Therapeutic Heparin	Superior Sagittal Sinus	Hemorrhagic Infarction	Brain Death
Thompson, et al.[93]	50, M	Respiratory	Prophylactic enoxaparin	Superior Sagittal, Left Transverse, Left Sigmoid, Vein of Labbe	Small Lobar IPH	Discharged Home
Ren, et al.[80]	53, F	Respiratory (Intubated)	Unknown	Cortical Venous Thrombosis	Cortical SAH	Death (Autopsy report)
Bolaji, et al.[15]	65, M	Neurologic (hemiparesis)	None	Superior Sagittal, Right transverse, Right sigmoid	IPH	Rehabilitation
Hussain, et al.[46]	30, M	Neurologic (Seizure)	None	Torcula, Transverse sinus, Sagittal sinus	Lobar IPH	Discharged
Luzzi, et al.[62]	–	Neurologic	None	Transverse and Sigmoid Sinus	Spontaneous SDH	Discharged
Loos, et al.[61]	44, F	Neurologic	None	Inferior Sagittal Sinus, Straight sinus, Internal cerebral veins, Vein of Rosenthal	Bilateral IPH	Remains hospitalized (improving)
Beretta, et al.[13]	62, F	Neurologic	None	Superior Sagittal Sinus, Straight Sinus, Transverse sinus, Vein of Galen, Bilateral internal cerebral veins	Sulcal SAH	Rehabilitation
Bastidas, et al.[47]	13, F	Neurologic (Headache, vomiting)	None	Bilateral transverse sinus and Right sigmoid sinus	Occipital IPH	Discharged without deficit
Klein, et al.[55]	29, F	Neurologic (Seizure)	None	Transverse and sigmoid sinus	Hemorrhagic infarct	Discharged with neurologic deficits
Hemasian, et al.[45]	65, M	Neurologic	None	Transverse and sigmoid sinus	Hemorrhagic infarct	Recovered
Tu, et al.[96]	30′s, M	Neurologic (Seizure)	None	Transverse and Sigmoid sinus	Lobar IPH	Brain Death after Neurosurgical decompression

Table 5 (*continued*)

Patients with Active Covid-19 Infections						
Study	Age, Sex	Presenting Symptoms	Anticoagulation at the time of the CVT	CVT	Hemorrhage	Outcome
Patients with Recent Covid-19 Infection						
Study	Age, Sex	Interval Since Covid-19 Diagnosis	Presenting Symptoms	CVT	Hemorrhage	Outcome
Manral, et al.[64]	27, M	4 weeks	Hand weakness, Confusion	Cortical veins	IPH	Recovered
Dakay, et al.[27]	26, M	2 weeks	Hemiparesis, Headache	Superior sagittal sinus and vein of Trolard	IPH	Recovered
Khazaei, et al.[54]	57, M	3 weeks	Hemiplegia, Seizure	Transverse sinus and cortical veins	SAH and IPH	Discharged in Stable Condition
Saad, et al.[84]	30's, M	2 weeks	Seizure	Superior sagittal sinus to right IJV	SAH	Recovered

Abbreviations: CVT = cerebral venous thrombosis, M = male, F = female, IPH = intraparenchymal hemorrhage, SAH = subarachnoid hemorrhage, SDH = subdural hematoma.

those patients died (mortality rate 71%), and two were discharged to rehabilitation. Of those with primary respiratory symptoms, four were on some form of anticoagulation and/or antiplatelet medications. The most common combination of hemorrhages was IPH/SAH (N = 4), followed by IPH/SAH/SDH (N = 2) and SAH/SDH (N = 1).

One patient (36-year-old male) presented primarily with neurologic symptoms and was found to have a multicompartment hemorrhage (IPH/SAH/SDH).[5] He required neurosurgical decompression, and Covid-19 RNA was present in his cerebrospinal fluid (CSF). His outcome was not reported.

Hemorrhage related to cerebral venous thrombosis

There were 16 studies identified that included a total of 17 patients with either active or recent Covid-19 infection, who had cerebral venous thrombosis (CVT) associated with intracranial hemorrhage. There were also three large studies discovered by the search that reported statistics on patients with Covid-19 and cerebral venous sinus thrombosis (CVST). One study was done over nine months and identified eight patients that met this inclusion criteria, of which 2 had associated intracranial hemorrhage (25%). The authors also conducted a literature review on this topic and reported that 6 of the 33 patients identified in the literature had an associated intracerebral hemorrhage (18%). Another study conducted across three academic centers identified six patients with Covid-19 and CVST, of which four had associated hemorrhagic parenchymal lesions (66.7%).[75] The third study was done across nine tertiary care stroke centers and identified 13 patients with Covid-19 and CVST, of which four had associated IPH (31.7%).[71] Of note, the authors of that article report that this is the same rate of associated hemorrhage in a historical group of patients with CVST.

Patients with active Covid-19 infection

The literature search identified 12 studies with 13 patients, who had active Covid-19 infection and developed an intracranial hemorrhage related to a CVT (Table 5). The patients ranged in age from 13 to 75 years old, and 50% (6 of 12) were female. Four patients were in the hospital for respiratory symptoms related to Covid-19, of which three were intubated for respiratory failure. The remaining nine patients presented with neurologic symptoms and were found to have asymptomatic Covid-19. None of the patients that presented with neurologic symptoms were reported to be on anticoagulation. The most common thrombosis was found in the transverse and sigmoid sinus (N = 6), followed by superior sagittal sinus (N = 2), and the superior sagittal sinus extending to the transverse and sigmoid sinuses (N = 2). The most common associated hemorrhage was IPH (N = 6), followed by hemorrhagic infarct (N = 4).

Patients with recent Covid-19 infection

There were four studies that each reported on a single patient with a recent Covid-19 infection, who subsequently presented with CVT and associated intracranial hemorrhage (Table 5). All four were male patients, and they were between the ages of 27 and 57 years old. One patient had isolated cortical vein thrombosis, and the other three patients had sinus thrombosis. They presented

Table 6
Hemorrhage Related to Ischemic Stroke.

Simultaneous Ischemic Stroke and Intracranial Hemorrhage					
Study	Age, Sex	Anticoagulation	Infarcted Area	Hemorrhage	Outcome
De Castillo, et al.[29]	64, M	None (presented with neurologic symptoms)	Thalamic and Temporal/ Occipital lobe	Parietal SAH	Discharged (mRS 4)
Kaushik, et al.[50]	5, M	Therapeutic anticoagulation for ECMO	ACA and MCA territory infarct	SAH	Brain Death
Hemorrhagic Conversion of Ischemic Stroke					
Study	Age, Sex	Anticoagulation	Infarcted Area	Hemorrhage	Outcome
Melegari, et al.[67]	55, F	Prophylactic LMWH	Temporal and Parietal lobe	Occipital and Temporal Lobe	Brain Death
Vacaras, et al.[98]	50, M	Had been on Prophylactic Enoxaparin 2 days prior	Multifocal in Bilateral Hemispheres	Multifocal with SAH	Discharged Home
Fayed, et al.[36]	71, M	None	Occipital Lobe	Occipital Lobe	Death from Multi-organ failure secondary to DIC

Abbreviations: M = male, F = female, SAH = subarachnoid hemorrhage, ACA = anterior cerebral artery, MCA = middle cerebral artery, mRS = modified Rankin Score.

2–4 weeks following a Covid-19 infection, and all four patients recovered.

Hemorrhage related to ischemic stroke

Simultaneous ischemic stroke and intracranial hemorrhage

There were five studies that described Covid-19 positive patients with simultaneous ischemic stroke and intracranial hemorrhage, four of which reported the incidence (Table 6). A large retrospective study across 11 New York hospitals looked at the rate of hemorrhagic conversion after ischemic stroke in 10,596 hospitalized Covid-19 patients.[49] They reported that 86 (0.81%) had an ischemic stroke, and that eight of those patients had evidence of simultaneous hemorrhage (0.08%). A second study from a single New York stroke center prospectively followed eight hospitalized Covid-19 patients with ischemic stroke and reported that two had an associated intracranial hemorrhage (25%).[4] Both patients had SAH secondary to cerebral artery dissection, and neither patient had any known risk factors. The third study reported that symptomatic Covid-19 patients with an ischemic stroke had a higher rate of associated intracranial hemorrhage than asymptomatic Covid-19 patients with ischemic stroke (31.7% vs. 4.4%).[48]

The remaining two studies reported two cases of Covid-19 patients with simultaneous intracranial hemorrhage and ischemic stroke (Table 6). One was a 64-year-old Covid-19 positive male that presented with neurologic symptoms and was found to have ischemic strokes in the thalamus, temporal lobe, and occipital lobe.[29] He had an associated SAH and was discharged home. The second was in a 5-year-old male on ECMO for Covid-19, who developed a large infarct in the ACA and MCA territory.[50] He had an associated SAH and progressed quickly to brain death.

Hemorrhagic Conversion of Ischemic Stroke

The search resulted in six studies discussing hemorrhagic conversion of ischemic stroke in patients with Covid-19, three of which analyzed the incidence of these bleeds (Table 6). The large retrospective study mentioned in the previous section of 10,596 hospitalized Covid-19 patients reported that of the 86 with an ischemic stroke, six had evidence of hemorrhagic conversion (0.06%).[49] The second study included 34 S centers in Europe, and reported data on 93 Covid-19 patients, who underwent mechanical thrombectomy for large vessel occlusions.[18] Of those 93 patients, 23 (25%) had intracranial hemorrhagic conversion within 30 days of MT, and five (5%) were symptomatic. The third study was a case series of 22 Covid-19 patients with acute cerebrovascular disease. They reported that three of the 22 (13.6%) suffered hemorrhagic conversion, and all required neurosurgical decompression.[92]

The remaining three studies describe three total cases of Covid-19 patients, who suffered hemorrhagic conversion of an ischemic stroke (Table 5). Two patients were intubated for Covid-19 at the time, and one presented with neurologic symptoms two days after being discharged. One patient was on prophylactic anticoagulation at the time of the stroke. One patient died from the stroke, and one patient died from multi-organ failure related to disseminated intravascular coagulation.

4. Discussion

This article provides a systematic review of nearly 100 PubMed indexed articles on the association between Covid-19 and intracranial hemorrhage. Among all hospitalized Covid-19 patients, the rate of intracranial hemorrhage is reported here to be between 0.1% and 3.3%, and it likely increases for patients>80 years old. The data reviewed here suggests that the development of an intracranial hemorrhage during Covid-19 infection is associated with increased rates of morbidity. These patients have a longer length of hospital stay, are more likely to require ICU level care, are more likely to have longer lengths of ICU stay, are more likely to require mechanical ventilation, and are more likely to require vasopressor support.[31,79] They also have an exceptionally high mortality rate, which is reported in articles included here to be 42–84%.

Nearly all subtypes of intracranial hemorrhage were represented in this literature review, including SAH (both aneurysmal and spontaneous), IPH, SDH, MCH, hemorrhage related to cerebral venous thrombosis, simultaneous hemorrhage with ischemic stroke, and hemorrhagic conversion of ischemic stroke. This suggests that although Covid-19 is associated with an increased risk of intracranial hemorrhage, there does not appear to be a predisposition for a specific subtype of hemorrhage. This also serves to highlight the point that not all intracranial hemorrhage during Covid-19 infection can be attributed to the pathology of the virus. It remains critically important to rule out other etiologies of intracranial hemorrhage in these patients, such as aneurysms, vascular malformations, underlying lesions, and underlying coagulopathy, in order to provide appropriate treatment.[2,26,99]

The risk factors for developing an intracranial hemorrhage during a Covid-19 infection include therapeutic anticoagulation and mechanical ventilation.[8,68] There also appears to be an increased rate of mortality for patients who develop an intracranial hemorrhage while on ECMO for Covid-19. Unfortunately, these risk factors may be necessary treatment modalities for Covid-19 infections. Mechanical ventilation and ECMO are often employed in Covid-19 due to acute respiratory distress syndrome, and therapeutic anticoagulation has been shown to improve outcomes in non-critically ill Covid-19 patients.[59] Thus, when caring for Covid-19 patients, careful consideration of the nuanced risks and benefits of these various treatment modalities is clearly necessary.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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